REMARKS

This supplemental amendment is being submitted to delete the paragraph preceding the conclusion of the amendment. This informality is the result of an inadvertent typographical error. The remarks set forth in the Amendment and Reply Under 37 C.F.R. 1.111 filed on July 10th and July 3rd are incorporated and support the minor corrections submitted herein. The Office Action mailed January 3, 2001 has been reviewed and the comments of the Patent and Trademark Office have been considered. Claim 22 was amended. Support for the present claim can be found, for example, on page 11 at lines 23-27. New claims 43 to 50 were added. Support for the new claims can be found, for example, at page 7 line 8 to page 8 line 11, page 9 lines 6-9, and page 11 lines 1-16. Claims 22-28 and 43-50 are pending for consideration.

Specification

The specification was amended as suggested by the Examiner in order to receive the benefit of an earlier filing date.

Rejections under 35 U.S.C. § 112, first paragraph

Claim 22 is rejected under 35 U.S.C. § 112 first paragraph due to an alleged lack of enablement for parathyroid hormone (PTH) derivatives recited by the claim.

The rejection asserts that the current application lacks the "guidance for making" these PTH derivatives. The rejection alleges that "(t)he skilled artisan is left to unduly extensive, random, trial and error experimentation in order to obtain such useful 'derivatives'." The rejection further contends that "there is a lack of predictability in the art."

PTH derivatives are well known in the art

This rejection is based on the assumption that there was no prior art concerning PTH derivatives. This is not the case. In fact, Potts et al. state that from 1973-1991 hundreds of PTH derivatives and fragments were synthesized that possessed the biological

activity of full length PTH (Potts et al., Journal of Endocrinology, 154, s15-s21, 1997). Similarly, during this time a number of PTH derivatives and fragments were synthesized that lacked biological function. From these experiments the minimal amino acid sequence required for the biological activity of the full length PTH protein was defined. In addition, Potts et al. described a number of amino acid residues that showed evolutionary conservation Potts et al., ENDOCRINOLOGY (3rd ed.), vol. 2 at pages 920-966 (1996). Such evolutionary conservation is known by those of skill in the art to be indicative of residues that are required for biological activity. Due to the extensive amount of information concerning the structure function relation of PTH at the time of filing, one of skill could easily produce a PTH derivative with the biological activity of the full-length PTH protein. Thus, this rejection is without merit and should be withdrawn.

In addition, new claim 45 relates to a subgroup of PTH derivatives with the biological activity of the full length PTH protein. As with claim 22, given the scope of the prior art, one skilled in the art would have no difficulty creating such a PTH derivative.

Rejections under 35 U.S.C. § 112, second paragraph

The rejection states that claim 22 is rejected under 35 U.S.C. § 112 second paragraph for the use of "indefinite language.

First, the rejection states that "a parathyroid hormone" is indefinite since "it is unclear if parathyroid hormone or some other hormone present in or secreted from the parathyroid gland is intended." Applicants are unaware of any hormone other than parathyroid hormone that is secreted by or found in the parathyroid gland. Thus, those skilled would realize that "a parathyroid hormone" means the same as "parathyroid hormone." Therefore, applicants respectfully submit that the rejection is unsubstantiated and should be withdrawn. In any event, Applicants do not believe the rejection applies to the present claim.

Similarly, the rejection alleges that the term "an effective amount of" is indefinite since "it is unclear what effect is intended by an 'effective amount.'" Claim 22 recites the

phrase "(a) method for increasing tooth movement comprising administering to a subject in need thereof an effective amount of a parathyroid hormone." Give the context, the term "effective amount" clearly refers to an amount of a parathyroid hormone required to effect tooth movement. As a result, this rejection is also without merit and should be withdrawn. In any case, Applicants believe the rejection moot in light of present claim 22.

Rejection under 35 U.S.C. §102(b):

Summary of Applicants' invention

The present invention concerns clinical methodology "for increasing tooth movement comprising administering to a subject in need thereof an effective amount of a parathyroid hormone (PTH) or PTH derivative thereof." As shown in Example 1 and Figure 3 the interdental distance is increased in subjects following the administration of PTH relative to those in a control group. Accordingly, the claimed method finds application in the field of clinical orthodontics.

Kamata does not teach every element of the claimed invention

Claim 22 is rejected under 35 U.S.C. §102(b) as being anticipated by Kamata. According to the rejection "Kamata teaches a method comprising administering an effective amount of a parathyroid hormone or a derivative thereof to rat." The rejection then asserts that "(t)he rats are subjects in need of increasing tooth movement, absent evidence to the contrary."

Contrary to the rejection's allegation, Kamata describes the administration of **parathyroid extract** to **parathyroidectomized** rats. Kamata proceeds to show that when mechanical force is applied to upper molars of these rats, there is an increase in the number of osteoclast associated with the molars relative to parathyroidectomized rats that were not administered the parathyroid extract.

Clearly Kamata fails to teach each and every aspect of Applicants' invention. As explained above, Kamata does not teach the administration of parathyroid hormone.

Rather, **Kamata teaches the administration of parathyroid extract**. There is no indication of the purity of this extract, particularly as to whether it contained impurities that might be responsible for the results in this disclosure. Furthermore, there is no reason to believe that the parathyroid extract would have contained a PTH derivative as alleged by the rejection. For this reason alone the rejection is incorrect and should be withdrawn.

In any event, despite the rejection's allegation, there is no indication that the rats described in Kamata were in need of tooth movement. According to Kamata, in the third full paragraph on page 412, the rats used were "Wistar strain male healthy rats." In fact, Kamata provides no description or suggestion regarding the practical application of PTH or PTH derivatives in the field of clinical orthodontic. Indeed, Kamata only administers parathyroid extract to parathyroidectomized rats. It is clear from the disclosure that the purpose of the administration of the parathyroid extract is to examine its role in bone resorption. In light of this fact as well, the rejection is without merit and should be withdrawn.

Similarly, Kamata does not provide any evidence of tooth movement resulting from the administration of PTH or PTH derivatives. Following the administration of parathyroid extract and the application of mechanical force to the molars of parathyroidectomized rats, Kamata does observe that the molars displayed a tension side and a compression side. However Kamata does not describe any difference in the movement of teeth in those animals administered the parathyroid extract relative to a control group that did not receive the parathyroid extract. Instead, Kamata examines the histological changes associated with parathyroid extract in parathyroidectomized rats. In contrast, Applicants describe the effect on interdental distance following the administration of PTH as previously discussed. Therefore, the rejection cannot be sustained for this reason also and should be withdrawn.

In view of the above, Applicants' believe the present invention is clearly different from that of Kamata and respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. §103(a):

The rejection states that claims 22-28 are rejected under Rejection under 35 U.S.C. §103(a) in view of Gianelly, Kronenberg, Gardella, and Sindrey. The rejection states that "Gianelly teaches that it appears possible to enhance orthodontic tooth movement by the local use of parathyroid hormone." Kronenberg and Gianelly describe various PTH derivatives. Sindrey teaches the purification of PTH. The rejection alleges that "it would have been obvious to one of ordinary skill at the time of Applicants' invention to enhance orthodontic tooth movement by the local use of parathyroid hormone as taught by Gianelly. The rejection then contends that it would have been obvious to use purified PTH or PTH derivative as taught by the combination of Kronenberg, Gardella, and Sindrey "with a reasonable expectation of success.

The rejection, however, errs in relying on Gianelly to suggest that PTH could be used clinically to enhance orthodontic tooth movement. This reference states that "the left lateral incisors of rats treated with parathyroid hormone moved significantly farther from the midline than the right lateral maxillary incisors." Gianelly implies that PTH can be used in order to increase tooth movement in a subject in need thereof, however they provide no evidence to suggest that a single injection of PTH is sufficient for an orthodontic remedy. In fact, the combination of references fails to suggest the benefit of multiple or continuous administration of PTH or of a PTH derivative as an orthodontic remedy.

On the other hand, Applicants have quantified the effect of the continuous administration of PTH on tooth movement. They have shown that an increase in the dose of PTH results in an increase in tooth movement as shown in Figure 2. Similarly, they have shown the benefit in tooth movement that results from the administration of PTH over time, for example, in Figure 5. Applicants believe that these data clearly establish the benefits of the use of multiple or continuous administrations of PTH or a PTH derivative for an orthodontic treatment.

Similarly, new claims 47 and 49 recite orthodontic remedies that entail the administration of preparations comprising PTH or PTH derivatives for sustained release and systemic delivery respectively. There is no suggestion or motivation provided by the cited combination of references for these aspects of the present invention.

In light of these comments, applicants believe that the rejection of claims 22 to 28 under 35 U.S.C. §103(a) has been overcome.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully submit that all of the pending claims are now in condition for allowance. An early notice to this effect is earnestly solicited. If there are any questions regarding the application, the Examiner is invited to contact the undersigned at the number below.

Respectfully submitted,

Date 4 September 2001 By S. A. Bent

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Versions with Markings to Show Changes Made

In the Specification:

On page one after the Title claim for priority has been added.

In the Claims:

Please amend claim 22 as follows:

22. (Amended) [A method for increasing tooth movement] An orthodontic remedy comprising administering , multiple times or continuously, [to a subject in need thereof] an [effective] amount of [a] parathyroid hormone or of a parathyroid hormone [a] derivative [thereof] that has the same biological effect as full length PTH, that results in an increase in tooth movement in a subject in need thereof.